Self-experience in the early phases of schizophrenia: 5-year follow-up of the Copenhagen Prodromal Study

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Despite the avalanche of empirical data on prodromal/"at risk" conditions, the essential aspects of the vulnerability to the schizophrenia spectrum remain largely unaddressed. We report here the results of the Copenhagen Schizophrenia Prodromal Study, a prospective, observational study of first admission patients in putative state of beginning psychosis (N=151) with a follow-up length of 60 months. At follow-up, the rate of conversion to schizophrenia spectrum diagnosis was 37%, whereas the conversion rate from schizotypal disorder to schizophrenia was 25%. High levels of perplexity and self-disorders baseline scores yielded the best prediction of the subsequent development of schizophrenia spectrum disorders. Escalating transitions within the spectrum (i.e., from schizotypal disorder to schizophrenia) were not associated to any candidate psychopathological predictor.

Key words: Schizophrenia spectrum, schizotypal disorder, psychosis, diagnostic stability, prodrome, vulnerability, anomalous subjective experiences

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In most of the Western world, several projects are being implemented, focusing on the pre-onset identification and early treatment of schizophrenia and other psychoses, based on the assumption that untreated illness becomes more chronic, socially invalidating and treatment resistant (1-4). In this context, subtle (non-psychotic) qualitative anomalies of subjective experience (such as disorders of affect, perception, bodily experience, cognition, volition and action) have regained the status of potential precursors of schizophrenia, and specific subsets of these anomalies (e.g., at risk basic symptoms) have been proposed for the pragmatic purposes of early detection (5-9).

Our research programme, in continuity with the Copenhagen high-risk, adoption, and linkage studies (10-16), focuses on trait features characteristic of the typical core of schizophrenia (17-19). We have studied in particular some alterations of the very experience of the self (i.e., self-disturbances, SDs). These comprise an unstable sense of self-presence and first person perspective, a lack of basic sense of self-identity, disturbances of the tacit fluidity of the field of awareness, hyper-reflexivity, and perplexity, i.e. a pervasive difficulty in grasping the familiar and taken for granted meanings (19-21). SDs are not to be considered as contingent symptomatic constellations, but rather express enduring, profound trait-like distortions of subjectivity, articulating specific, non-psychotic modes of experience (i.e., changes in the qualitative, first-personal givenness of experience) (19,20).

Our first empirical report on SDs (9) was based on explorative interviews with 19 first admission patients with the diagnosis of a schizophrenia spectrum disorder, and was supported by a similar report from Norway (8). We wished to replicate these findings in a systematic prospective study of consecutive first-admitted patients. We aimed to assess anomalies of subjective experience (including SDs), and their longitudinal association with the schizophrenia spectrum disorders. Moreover, we aimed to explore the diagnostic stability of schizophrenia spectrum (over an observation period of 5 years) and identify potential clinical-psychopathological predictors for intra-spectrum diagnostic spiralling (schizotypal disorder transiting to schizophrenia) and towards-spectrum diagnostic spiralling (i.e., incident cases of schizophrenia spectrum, either schizotypal disorder or schizophrenia).

METHODS

The sample consisted of 155 first-admission patients with age <40 years consecutively referred to the University Psychiatric Center Hvidovre, during the period from September 1, 1998 to September 1, 2000. The psychiatric center serves a catchment area of approximately 130,000 inhabitants, residing in the City of Copenhagen.

Exclusion criteria comprised a diagnosis of melancholia, bipolar disorder or organic brain disorder, primary or clinically dominating substance abuse, involuntary or forensic patient status. Severely psychotic, aggressive patients were first interviewed after initial stabilization.

The patients participated upon a written informed consent. Four patients were ultimately excluded because they were diagnosed with organic psychiatric disorder, undetected at the inclusion, leaving a total of 151 subjects.

At baseline, the patients were assessed with a semi-structured interview comprising overall psychosocial and family history (including second informant information), psychopathological anamnesis and psychodiagnostic assessment with a phenomenological exploration of anomalous subjective experiences (22,23). These were explored with the Bonn Scale for the Assessment of Basic Symptoms (BSABS) (24), expanded with additional items concerning self-experience

(23). All interviews were performed by a consultant psychiatrist with extensive research interview experience, who was trained in the use of BSABS by the Huber-Klosterkötter group in Germany. On the basis of all information, an ICD-10 operational research diagnosis was allocated by the interviewer after case discussion with another senior clinician.

Five years later, the sample was located through a national personal register (25) and invited to participate upon a written consent. The reassessment, blind to the information gathered at the initial assessment, repeated all the baseline interview components (22,23). Briefly, those included the OPCRIT Checklist (26), the BSABS (24), the Positive and Negative Syndrome Scale (PANSS) (27), and the DSM-III-R Severity of Psychosocial Stressors Scale: Adults (28). Expressive features (e.g., affect modulation, contact-quality, gaze, stereotypies, mannerisms, disorganization, and disorder of language) were coded on the mental status items, developed and used in the Copenhagen High Risk Study (13) and the Copenhagen Linkage Study (29,30). The re-assessment interviewer was a consultant psychiatrist with research experience. She allocated an ICD-10 research diagnosis at a case conference with another senior psychiatric clinician, who reviewed the chart material and witnessed the patient interviews. Reassessment diagnoses were lifetime and based only on the follow-up interview and chart material.

During the follow-up period, the patients adhered to their individual treatments led by clinicians in charge. Thus, treatment modalities and their efficacy were not part of the study.

An interrater reliability assessment between the two interviewing psychiatrists, checking all study instruments, was performed and demonstrated excellent reliabilities. For example, in the section dealing with anomalies of subjective experience, out of 41 items targeting perplexity, self-disorders and perceptual disorders, 16 had a very good kappa (i.e., above 0.81), 20 a good kappa (i.e., between 0.61 and 0.80), four had a moderate kappa (i.e., between 0.41 and 0.60) and one (diplopia/oblique vision) a fair kappa.

The diagnoses were grouped into three major categories: group 1 with schizophrenia/all non-affective, non-organic psychoses; group 2 with schizotypal disorder; and group 3, a miscellaneous category containing all other disorders outside the schizophrenia spectrum (e.g., panic disorder, major depression, obsessive-compulsive disorder).

We adopted a dimensional approach to characterize the psychopathological profile in terms of both major diagnostic symptoms (i.e. positive, negative, formal thought disorder, affective-anxious) and anomalous subjective experiences. These experiences were grouped in three *a priori* scales: perplexity, self-disorders, perceptual disorders. Briefly, "perplexity" addresses a sense of lacking immersion in the world, lack of spontaneous grasping of commonsensical meanings, puzzlement, and alienation; "self-disorders" maps anomalies of pre-reflective self-awareness, i.e., of the tacit sense of existing as a self-coinciding subject of experience and action; "perceptual disorders" encompasses a wide variety of non-psychotic perceptual (mostly visual-acoustic) aberrations.

SAS 9.1 version was used with both parametric and non-parametric and uni- and multivariate approaches. Diagnostic transitions were charted graphically. Predictors of diagnostic transitions of escalating severity (i.e., intra-spectrum from schizotypal disorder to schizophrenia, and towards-spectrum from other diagnosis to schizotypal disorder or schizophrenia) were weighted by binary logistic regression.

RESULTS

Baseline socio-demographic, clinical and psychopathological features of the sample are reported in Table 1. Whereas PANSS scores decreased linearly from schizophrenia to non-spectrum disorders (with schizotypal disorder in intermediate position), this was not the case for anomalous subjective experiences (schizophrenia and schizotypal disorder had comparable scores, which were significantly higher than those of non-spectrum disorders).

The full face-to-face reassessment interview was obtained

Table 1 Baseline profiles of the diagnostic subgroups: socio-demographic and psychopathological features

	Schizophrenia/ Psychoses (N=51)	Schizotypal disorder (N=50)	Other psychiatric disorder (N=50)	p
Age at inclusion (mean±SD)	25.3±5.0	24.6±4.4	26.2±4.6	0.183
Male/female	26/25	14/36	17/33	0.059
Age of illness onset (years, mean±SD)	20.9±6.3	17.5±5.2	18.7±6.0	0.028
Duration of illness (months, mean±SD)	54.6±59.2	84.4±60.9	90.8±77.7	0.008
Duration of untreated psychosis (months, mean±SD)	27.3±42.9	-	-	-
PANSS positive symptoms (mean±SD)	19.06±5.8	11.9±3.1	9.1±2.3	<0.0001
PANSS negative symptoms (mean±SD)	16.95±6.06	13.3±4.0	9.7±3.3	<0.0001
Formal thought disorders (mean±SD)	4.31±3.07	2.8±2.3	1.0±1.5	<0.0001
Anxiety and affective symptoms (mean±SD)	5.91±3.60	8.6±3.2	7.8±3.3	0.0003
Perplexity (mean±SD)	5.27±4.39	5.63±3.3	2.4±3.1	<0.0001
Self-disorders (mean±SD)	9.59±6.11	9.4±4.8	4.2±4.2	<0.0001
Perceptual disorders (mean±SD)	2.99±3.41	2.6±3.0	1.0±1.5	0.0008

PANSS – Positive and Negative Syndrome Scale
Statistical test: Kruskal-Wallis (non-parametric ANOVA) or X-square when appropriate

in 99 patients (64%). Four patients (3%) declined personal interview but accepted a telephone interview. Nineteen patients refused (12%) but could be followed-up and reassessed through the chart material over the entire 5 years period. Thus, of the initial sample of 151 patients, 121 (80%) could be rediagnosed. There were no differences in age, gender or education between the interviewed and non-interviewed groups. The groups did not differ with respect to the diagnosis at the initial assessment. However, the non-interviewed patients more often reported substance abuse at the initial assessment (p=0.02). For the personally re-interviewed patients, the mean and median follow-up periods were 1889 and 1811 days, respectively (approximately 5 years, range: 1334-2571 days).

Table 2 and Figure 1 show the diagnostic changes over the 5-year follow-up period. The overall kappa value of agreement for the three diagnostic groupings across the first and the follow-up assessments is 0.64, which reflects a rather pronounced stability.

Within group 1, five patients, initially diagnosed with acute non-affective psychosis, were rediagnosed with paranoid schizophrenia. Only three patients left the group 1: one, originally diagnosed with hebephrenic schizophrenia, was rediagnosed as suffering from a schizotypal disorder; another patient with acute non-affective psychosis was rediagnosed with bipolar disorder; a third patient with schizophrenia was rediagnosed as suffering from a psychotic depression. Thus, of the 43 patients originally in group 1, 40 still remained there at the follow-up (93%).

Group 2 also manifested a relative stability of diagnosis. Ten schizotypal patients (25%) were rediagnosed with schizophrenia 5 years later, one with affective disorder (depression) and one with borderline personality disorder (hence only 5% exited from the schizophrenia spectrum).

From group 3, two patients (originally with mixed and borderline personality disorder) were rediagnosed with schizophrenia. Twelve additional patients (initially diagnosed with depression, n=3, or mixed, borderline or unspecified personality disorder, n=9) were rediagnosed with schizotypal disorder.

Schizotypal patients rediagnosed with schizophrenia were 25% of the original group. Logistic regression analysis contrasting these patients and the other 30 who did not change their diagnostic status revealed no significant influence of any baseline variable (i.e. age, sex, psychopathological dimensions, anomalous subjective experience, total number of individual schizotypal criteria).

In total, 14 incident cases with a schizophrenia spectrum disorder were diagnosed at the follow-up. Logistic regression analysis (comparing these 14 individuals with the individuals remaining in group 3) revealed that high baseline scores on self-disorders and perplexity predicted a subsequent evolution of the schizophrenia spectrum disorder (self-disorders: Fischer's exact p=0.003, OR=12.00; 95%CI 2.15-67.07; perplexity: Fischer's exact p=0.02, OR=6,11; 95%CI 1.34-27.96). The PANSS measures were not predictive and the transition was gender- and age unrelated (Table 3).

Table 2 Changes in lifetime diagnoses from inclusion to follow-up

		BASELINE			
		Schizophrenia/ Psychoses	Schizotypal disorder	Other psychiatric illness	Total number
FOLLOW-UP	Schizophrenia/ Psychoses	40	10	2	52
	Schizotypal Disorder	1	28	12	41
	Other psychiatric Illness	2	2	24	28
	Total number	43	40	38	121
	Drop-outs	8	10	12	30

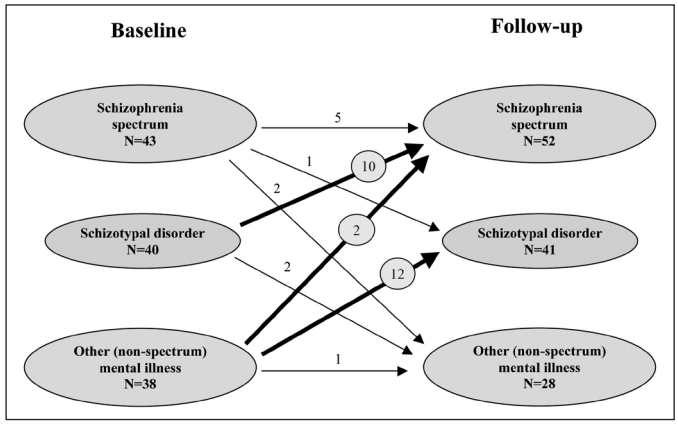

Figure 1 Diagnostic fluxes

DISCUSSION

The pragmatic diagnostic partition based on ICD-10 schizophrenia/non-affective psychosis, schizotypal disorder and other psychiatric illness revealed an overall high stability over 5 years (kappa=.64). The stability was higher for the diagnosis of schizophrenia (93%) than for schizotypal disorder (70%) and the diagnostically miscellaneous category "other psychiatric illness" (63%).

One fourth of the schizotypal patients were rediagnosed with schizophrenia at follow-up. However, none of the baseline socio-demographic or psychopathological variables (including the number and the frequency of individual schizotypal criteria) was predictive of this outcome. This suggests that these two spectrum phenotypes (schizotypal disorder and schizophrenia) are more dissimilar in degree than in kind. Concretely, schizotypal disorder appears to be a subpsychotic condition, in many respects similar to schizophrenia. The ICD-10 category of schizotypal disorder seems to diagnose severely ill clinical cases that do not fully meet the criteria for schizophrenia. Those prospectively rediagnosed cases with schizophrenia appear to cross the border, at any

Table 3 Binary logistic regression with diagnostic transition to schizophrenia spectrum as follow-up outcome

	Spectrum diagnostic conversion		No diagnostic conversion				
	High score (N)	**Low score (N)**	**High score (N)**	**Low score (N)**	**p**	**OR[a]**	**95%CI**
Symptom dimensions							
PANSS positive symptoms	8	6	13	11	1.00	1.13	0.30-4.26
PANSS negative symptoms	9	5	16	8	1.00	0.90	0.23-3.59
Formal thought disorder	8	6	10	14	0.50	1.87	0.49-7.08
Anxiety and affective symptoms	10	4	11	13	0.18	2.95	0.72-12.11
Anomalous subjective experiences							
Perplexity	11	3	9	15	**0.02**	**6.11**	**1.34-27.96**
Self-disorders	12	2	8	16	**0.003**	**12.00**	**2.15-67.07**
Perceptual disorders	8	6	8	16	0.19	2.67	0.69-10.36
	26-38 years (N)	**19-25 years (N)**	**26-38 years (N)**	**19-25 years (N)**		**OR[b]**	
Age at inclusion	6	8	15	9	0.32	0.45	0.12-1.72
	Male (N)	**Female (N)**	**Male (N)**	**Female (N)**		**OR[c]**	
Gender	5	9	8	16	1.00	0.90	0.23-3.59

Significant results in bold; p-value from Fischer's exact test for independence between changing/keeping diagnose and scoring high/low
OR[a] – odds ratio if the scale score is high; OR[b] – odds ratio if age is 26-28 years; OR[c] – odds ratio if gender is female

moment of their clinical history, by a contingent intensification of this or that symptom (e.g., from constricted to flat affect; from privately experienced to publically accessible audible thoughts). Such considerations cohere with the recent findings of the NAPLS study, rediscovering (DSM-IV) schizotypal personality disorder as a possible "independent risk syndrome for psychosis" (31), and another Danish study (OPUS), which reported comparable diagnostic conversion rates from ICD-10 schizotypal disorder to schizophrenia (32).

Above one third of the subjects receiving a non-spectrum diagnosis at baseline were rediagnosed within the schizophrenia spectrum five years later. On the contrary, only 5% of subjects originally allocated in the schizophrenia spectrum were rediagnosed outside that category at the follow-up. With respect to the incident cases of schizophrenia spectrum, the comparison with the individuals remaining in the initial group indicated two clusters of anomalous subjective experiences that were predictive of the diagnostic transition: self-disorders and perplexity. None of the PANSS scores was associated with increased risk of transition. Overall, this indicates that self-disorders and perplexity capture rather essential features of the spectrum-proneness among clinical phenotypes. This is in line with converging evidences from other quantitative (16,33,34) and quali-quantitative (8,9,35) studies.

The results of the study must be viewed through some contextual limitations. The sample was based on referrals to a hospital-based inpatient unit. Hence the "caseness" (severity) threshold for referrals is probably higher than that associated to outpatient service admissions. Therefore, the sample features might be of limited generalizability to mental health systems with rich, easily accessible outpatient psychiatric services. Furthermore, we adopted diagnostic stability and transition within the ICD-10 categories as outcome variables. In particular, the incident cases of schizophrenia spectrum diagnosis ("transition to the schizophrenia spectrum") constitutes a clinically and conceptually different construct than the "transition to psychosis" which is the typical outcome in prodromal/ultra-high-risk research (where psychosis threshold is conceived as a quantitatively defined severity cut-off point of positive psychotic symptoms) (36). Finally, the data collection is based on the two chronological nodes – baseline and five-year reassessment – and is therefore unsuitable to track a more fine-grained timing of the transitions related to relapse and possible readmission. In this respect, it must be emphasized that, whereas the baseline assessment was related to consecutive referrals and, therefore, coinciding with severe and acute psychopathological states, this was not the case for the reassessment 5 years apart, which is an arbitrary point in the natural history of the illness (37).

CONCLUSION

In conclusion, our results indicate that certain trait-like anomalous subjective experiences, particularly self-disorders and perplexity, could be important prognostic indicators for identifying (within newly admitted subjects) those with vulnerability traits of a schizophrenia spectrum disorder. Crucially, none of the canonical psychopathological dimensions that are usually considered as a core assessment standard of schizotropic symptomatology (e.g., positive, negative, disorganized symptoms) showed any predictive power. The results also indicate that about one fourth of the subpsychotic configurations of the schizophrenia spectrum intercepted by the ICD-10 diagnosis of schizotypal disorder are rediagnosed with schizophrenia within five years. This suggests that the current ICD-10 definition of schizophrenia relies on symptoms and signs set at a very high level of severity (and chronicity). Consequently, in a clinical setting, the category of schizotypal disorder includes less symptomatic, subthreshold patients, who would have been considered by the ICD-8 as suffering from non-paranoid or beginning paranoid schizophrenia (38-40).

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